REMARKS

Claims 23, 25-30 and 32-49 are pending in the subject application. By this Amendment, applicants have canceled claims 25 and 26 without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in this or a later application, and amended claims 23, 27 and 48.

Applicants note that the amendments to claim 23 are fully supported in the specification at, *inter alia*, page 15, lines 15-25; page 16, line 3 and lines 9-10; page 22, lines 23-25; page 56, lines 17-20; and page 58, lines 27-30. Thus, applicants maintain that these amendments do not raise any issue of new matter. The amendments to claim 27 merely change its dependency, as necessitated by the cancellation of claim 26 from which it formerly depended, and clarify that it is the PA14 hybridoma, rather than PA14 antibody, which was deposited with the American Type Culture Collection (ATCC). This amendment relating to the PA14 hybridoma is supported in the specification at, *inter alia*, page 15, lines 15-25). The amendments to claim 48 merely convert it to a dependent claim, dependent from claim 23, and are supported in the specification at, *inter alia*, page 10, lines 4-15 and Fig. 6D; and page 54, line 32 to page 55, line 16. Thus, the amendments to claims 27 and 48 also raise no issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 23, 27-30 and 32-49, as amended, will be pending and under examination.

The Invention

The invention claimed in the subject application provides methods of reducing HIV-1 viral load in an HIV-1-infected subject which comprises administering to the subject solely after viral steady

state is reached an effective viral load-reducing amount of an IgG monoclonal antibody (mAb). This mAb is PA14, produced by the hybridoma cell line designated PA14 (ATCC Accession No. HB-12610), or an antibody that cross-competes with mAb PA14 for binding to the CCR5 receptor. The mAb also binds to the CCR5 chemokine receptor, inhibits binding of HIV-1_{JR-FL} gp120/sCD4 complex to CCR5 receptors on the surface of $CD4^{-}CCR5^{+}$ cells, and inhibits fusion of HIV-1 to $CD4^{+}CCR5^{+}$ cells, thereby inhibiting repeated infection of the subject's cells and reducing the subject's HIV-1 viral load to 50% or less of the HIV-1 viral load prior to administration of any of the antibody to the subject.

Rejections under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 23, 25, 26, 28-30, and 32-39 under 35 U.S.C. §112, first paragraph, as enabling for administering antibody PA14 to reduce HIV viral load when administered solely after viral steady state is reached, but allegedly not providing enablement for anti-CCR5 antibodies that reduce HIV viral load when administered solely after viral steady state is reached. The Examiner asserted that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The Examiner stated that "to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech Inc. v. Novo Nordisk*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); citing also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The Examiner also

cited *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), which states that:

> [f]actors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Examiner noted that a conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright,* 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The Examiner stated that, as applicants have argued in previous responses filed 8/25/03, 6/25/04, and 2/16/05, the art is uncertain as to the predictability of using antibodies to reduce HIV viral load when administered solely after viral steady state is reached. The Examiner noted that it would be expected that an antibody that binds to CCR5 and inhibits HIV binding to the receptor would do so at all times. However, the Examiner stated that the review of the art suggested by applicants indicates that this is not the case. The Examiner stated that, for example, applicants directed his attention to two prior art references, Gauduin et al. (1997) Nature Medicine 3: 1389-93 ("Gauduin") and Poignard et al. (1999) Immunity 10: 431-8 ("Poignard"). The Examiner noted that Gauduin and Poignard both disclose a potently neutralizing anti-HIV-1 antibody, IgGlbl2, that protects against infection with HIV-l if administered at the time of, or up to several (6-24) hours after, viral

challenge. The Examiner further stated that Poignard demonstrates, however, that the same antibody affords little or no therapeutic benefit in subjects in which the HIV-1 viral load had reached steady state levels prior to administration of the antibody.

The Examiner also stated that Gauduin teaches that although the IgGlb12 antibody was found to block infection when administered after HIV-1 challenge, this effect was obtained only when the antibody was administered no more than several hours after viral exposure, i.e., significantly before viral steady state was reached. The Examiner noted that, in contrast, claim 23 recites that the HIV-1 viral load of the HIV-1 infected subject is reduced when the antibody is administered "solely after viral steady state is reached."

The Examiner concluded that Poignard and Gauduin clearly support the contention that antibodies useful for prophylactic treatment when administered prior infection often do not protect against an established HIV-1 infection. Thus, the Examiner accepted applicants' arguments that (1) based on the prior art teachings of Poignard and Gauduin, one skilled in the art at the time the invention was made could not have predicted and certainly would not have had an expectation that treatment administered solely after viral steady state had been reached would be efficacious; and (2) one of ordinary skill in the art, armed with the knowledge that an anti-HIV-1 antibody that protects against acute HIV-1 infection may be ineffective against chronic HIV-1 infection, could not have predicted and would have had no reasonable expectation of success that an anti-CCR5 antibody would prove efficacious in reducing the viral load in chronically HIV-1-infected subjects with steady state HIV-1 levels.

The Examiner also accepted applicants' previous arguments that,

though the antibody of Poignard and Gauduin is directed to an epitope of HIV-1 gp120 whereas the antibodies recited in the instant claims are directed to an epitope of the CCR5 chemokine receptor, the identity of the antibodies is secondary to the general principle taught by the prior art references. The Examiner acknowledged that, indeed, Poignard's results on the effect of HIV-1 neutralizing antibodies in subjects with steady state HIV-1 levels are not limited to a particular antibody. The Examiner stated that, instead, these results "show that passive administration of either a single neutralizing human mAb or of a cocktail of three such Abs has minimal effect on the control of an ongoing HIV-1 infection in the hu-PBL-SCID mouse model" (citing page 434, first paragraph of the "Discussion" in Poignard). Thus, the Examiner agreed with applicants' contention that the more salient principle taught by Gauduin and Poignard is clearly that the prophylactic efficacy of an anti-HIV-1 antibody in protecting against acute HIV-1 infection is not predictive of therapeutic efficacy against a chronic HIV-1 infection, characterized by steady state viral levels, as claimed in the subject invention.

The Examiner stated that the above uncertainty is not remedied by applicants' specification which is lacking in working examples. According to the Examiner, the only working example, found on pages 96 and 97, is directed solely to testing the efficacy of mAb PA14. The Examiner stated that this example provides support for the claims limited to PA14, but, given the uncertainty of the art in regards to treatment with antibodies after viral steady state has been reached, does not provide support for the full scope of the claims. The Examiner concluded that, based on the evidence as a whole, and in light of the factors articulated by the court in *In re Wands*, the instant invention lacks an enabling disclosure.

In response, applicants respectfully traverse the above grounds of rejection. Applicants note that the legal standard for lack of enablement, as enunciated in *In re Wands*, is a requirement for undue experimentation, i.e., experimentation that is not routine. Applicants maintain, for the reasons set forth below, that the specification provides disclosures that enable one skilled in the art to perform the claimed invention without undue experimentation.

Applicants note that claims 25 and 26 have been canceled herein, thereby rendering their rejection moot. Applicants note also that claim 48 has been amended to now depend from claim 23, leaving claim 23 as the sole independent claim pending.

Applicants note that claim 23, as amended, provides a method of reducing HIV-1 viral load in a chronically HIV-1-infected subject, which method comprises administering to the subject an amount of an antibody, wherein the antibody is mAb PA14 or an antibody that cross-competes with PA14 for binding to the CCR5 receptor. Applicants refer to the Examiner's statement on page 8 of the Office Action that pages 96-97 of the specification provide support that enable claims directed to methods comprising the use of the PA14 antibody. Applicants maintain that the specification also provides enabling support for methods comprising the use of mAbs that cross-compete with PA14 for binding to the CCR5 receptor.

In this regard, applicants note that the specification describes several comparative assays on mAbs that were shown to inhibit HIV_{JR-FL} envelope-mediated fusion to $CCR5^+$ cells, i.e., the PA8, PA9, PA10, PA11, PA12, PA14 and 2D7 mAbs (see page 53, line 33 to page 54, line 3). The results of these assays indicate that PA14 and 2D7 exhibit similar functional characteristics that differ from those of the other antibodies tested. For example, in an

assay to quantify antibody binding to $CCR5^+$ cells, mAbs 2D7 and PA14 each stained >20% of mitogen-stimulated PBMC, whereas PA11 and PA12 stained ~10%, and PA8, PA9 and PA10 stained <5% of PBMC (see the specification at page 50, line 33 to page 51, line 1).

In epitope mapping of the mAbs using CCR5 alanine mutants, certain point mutations were found to reduce the binding of all of the mAbs to CCR5 by >50%. In general, PA8-PA12 were the most affected, whereas PA14 and 2D7 were the least affected by this class of mutants (see page 50, line 33 to page 52, lines 11-14).

In an assay to measure the effect of the mAbs on RANTES-induced Ca^{2+} mobilization, PA8, PA9, PA10, PA11 and PA12 did not inhibit Ca^{2+} fluxes, even at concentrations as high as 100 µg/ml (see page 53, lines 13-16), whereas both PA14 and 2D7 blocked Ca^{2+} mobilization (see page 53, lines 19-24; page 59, lines 4-8).

In an assay to measure the inhibition of CCR5 co-receptor function by the mAbs, the rank order of potency was 2D7 ~ PA14 > PA12 > PA11 > PA10 ~ PA9 ~ PA8. The IC_{50} values for PA14 and 2D7 were virtually identical, being 1.7 µg/ml and 1.6 µg/ml, respectively. For PA11 and PA12, the IC_{50} values were 25.5 µg/ml and 10.0 µg/ml, respectively, whereas no IC_{50} values could be calculated for PA8, PA9 and PA10, since these mAbs inhibited fusion by only 10-15% even at concentrations as high as 300 µg/ml (see page 54, lines 3-9). The use of a luciferase-based entry assay to measure the ability of the different anti-CCR5 mAbs to inhibit entry of a prototypic R5 virus, JR-FL, and a R5X4 virus, Gun-1, gave a similar rank order of potency as in the cell-cell fusion assay (see page 54, lines 13-27). PA14 and 2D7 also inhibited binding of $HIV\text{-}1_{JR\text{-}FL}$ gp120/sCD4 to L1.2-$CCR5^+$ cells with significantly less efficiency than did mAbs PA9, PA10, PA11 and PA12 (see page 55, lines 7-16; page 59, lines 27-31).

To determine the interactions of co-receptor-specific drug candidates with endogenous chemokines, CCR5 mAbs were assayed in combination with each other or with RANTES for their ability to inhibit CCR5-mediated cell fusion. Whereas mAb combinations were identified which were highly synergistic (PA12 and 2D7), moderately synergistic (PA12 and PA14), and additive (PA11 and PA12), the combination of PA14 and 2D7 was weakly antagonistic. These data indicate that PA14 and 2D7 cross-compete for binding to $CCR5^+$ cells (see page 56, lines 17-20). Additionally, the inhibition of chemokine-induced calcium mobilization by PA14 and 2D7 suggest that these two antibodies compete with CC-chemokines for binding to CCR5 (see page 58, lines 27-30). Indeed, the specification discloses that epitopes to which PA14 and 2D7 bind, though not identical, are located entirely or partially in the first ten residues of ECL2 (see page 58, lines 17-20; page 61, lines 10-15).

The data summarized above suggest that mAbs which cross-compete with PA14 for binding to CCR5 have similar functional properties to PA14. Further, these functional properties are distinct from the properties of other mAbs that inhibit CCR5-mediated cell fusion but do not cross-compete with PA14 for binding to CCR5. On this basis, applicants maintain that, similar to mAb PA14, a mAb which cross-competes with PA14 for binding to CCR5 will also be effective in reducing HIV-1 viral load in an HIV-1-infected subject when this mAb is administered to the subject solely after viral steady state is reached.

Applicants note that, with respect to the claimed invention, several of the *Wands* factors referred to by the Examiner have been satisfied. In this regard, applicants assert, first, that only routine experimentation is required for a skilled artisan to identify mAbs that cross-compete with PA14 for binding to $CCR5^+$ cells.

Second, applicants note that the specification provides detailed guidance on how such mAbs may be identified (see page 48, line 32 to page 49, line 12; page 51, line 31 to page 61, line 15).

Third, the specification also provides a working example of a mAb (2D7) which cross-competes with PA14 for binding to $CCR5^+$ cells.

Fourth, applicants note that the level of skill in the biotechnology arts is very high. See, for example, *Enzo Biochem, Inc. v. Calgene, Inc.* 188 F.3d 1362, (Fed. Cir. 1999):

> [T]he district court determined that a person of ordinary skill in the art would be 'a junior faculty member with one or two years of relevant experience or a postdoctoral student with several years of experience,' *see Enzo,* 14 F.Supp.2d at 567, and we discern no clear error in this determination.

Fifth, notwithstanding the unpredictability of the art, applicants have presented abundant evidence hereinabove which suggests that mAbs which cross-compete with PA14 for binding to $CCR5^+$ cells, will also be capable of reducing HIV-1 viral load in an HIV-1-infected subject when this antibody is administered to the subject solely after viral steady state is attained.

Sixth, applicants maintain that the invention embodied in claim 23 is not overly broad since it is directed to methods comprising the use of specific antibodies, i.e., mAb PA14 or defined mAbs which cross-compete with PA14 for binding to CCR5.

Based on the forgoing remarks, applicants maintain that the specification, at the time the application was filed, would have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. Thus, applicants maintain that independent claim 23 is fully enabled by the specification as filed. The Examiner is therefore

respectfully requested to reconsider and withdraw the grounds of the instant rejection.

Applicants note that claims 27-30 and 32-49, as amended, depend, directly or indirectly, from claim 23 and therefore necessarily possess all the elements of claim 33. Moreover, applicants maintain that none of claims 27-30 and 32-49 possess any elements that are not fully supported in the specification as filed. Accordingly, applicants maintain that the specification enables claims 27-30 and 32-49, and respectfully request that the Examiner reconsider and withdraw the instant "enablement" rejections of these dependent claims.

Objection

The Examiner objected to claim 27 as being dependent upon a rejected base claim, but stated that it would be allowable if rewritten in independent form.

In response, applicants note that claim 27, as amended, depends from claim 23. Applicants maintain that the amendment of claim 27 obviates the instant objection.

Conclusion

In view of the remarks made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the rejections set forth in the March 2, 2005 Office Action, and earnestly solicit allowance of claims 23, 27-30 and 32-49, as amended, now pending in the subject application.

Terminal Disclaimer

Applicants direct the Examiner's attention to U.S. Serial No. 10/116,797, filed April 5, 2002, and published March 6, 2003 as U.S. Application Publication No. 2003/0044411 A1, from which the subject application claims priority. Applicants note that U.S. Application Publication No. 2003/0044411 A1 was disclosed as reference 2 in the Supplemental Information Disclosure Statement included in applicants' February 14, 2005 Amendment. Applicants note also that the claims now pending in U.S. Serial No. 10/116,797 were disclosed as reference 31 in the same February 14, 2005 Supplemental Information Disclosure statement, and a copy of these claims was provided to the Examiner as Exhibit 21.

Applicants note that the claims pending in U.S. Serial No. 10/116,797 are related to those now being presented in the subject application. Applicants also note that Notice of Allowance was issued in connection with U.S. Serial No. 10/116,797 on June 9, 2005.

Recognizing that any patent which issues from U.S. Serial No. 10/116,797 and any patent which may issue from the subject application will likely contain claims directed to overlapping subject matter, applicants intend to file a Terminal Disclaimer in both U.S. Serial No. 10/116,797 relative to the subject application, and in the subject application relative to U.S. Serial No. 10/116,797.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this

Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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